Armed Forces College of Medicine

AFCM

IMMUNOSUPPRESSANTS

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1.Classify immunosuppressant drugs.

2.Identify the benefit of using combinations of different immunosuppressant drugs.

3.Describe pharmacokinetics of calcineurin inhibitors and immunosuppressive antimetabolite.

4.Discuss mechanism of action, therapeutic uses of calcineurin inhibitors, immunosuppressive antimetabolite and corticosteroids.

5.List the adverse effects and drug interaction of calcineurin inhibitors and immunosuppressive antimetabolite.

6.Identify the drug interactions of calcineurin inhibitors and immunosuppressive antimetabolite.

The importance of the immune system in **protecting** the body against harmful foreign molecules is well recognized. However, in the case of organ transplantation, the immune system can elicit a damaging immune response, causing **rejection** of the transplanted tissue.

Because of their severe toxicities when used as monotherapy, **a combination** of immunosuppressive agents, usually at lower doses. Immunosuppressive drug regimens usually consist of anywhere from **two to four agents** with different mechanisms of action that disrupt various levels of T-cell activation.

IMMUNOSUPRESSIVE DRUGS

I. Selective Inhibitors Of Cytokine Production and Function
(Calcineurin inhibitors)

II. Immunosuppressive Antimetabolite
A.Azathioprine
B. Mycophenolate Mofetil

III. Inhibitors of cytokine gene expression
(Corticosteroids)

I. Selective Inhibitors Of Cytokine Production and Function

A. Cyclosporine

Mechanism of action:

- After diffusing into the T cell, *cyclosporine* binds to a **cyclophilin** (more generally called an **immunophilin**) to form a complex that binds to calcineurin.
- Calcineurin is responsible for dephosphorylating **NFATc** (**c**ytosolic **N**uclear **F**actor of **A**ctivated **T** cells). Because the **cyclosporine–calcineurin complex** cannot perform this reaction, NFATc cannot enter the nucleus to promote reactions that are required for the synthesis of cytokines, including IL-2.
- The end result is a **decrease in IL-2**, which is the primary chemical stimulus for increasing the number of T lymphocytes.

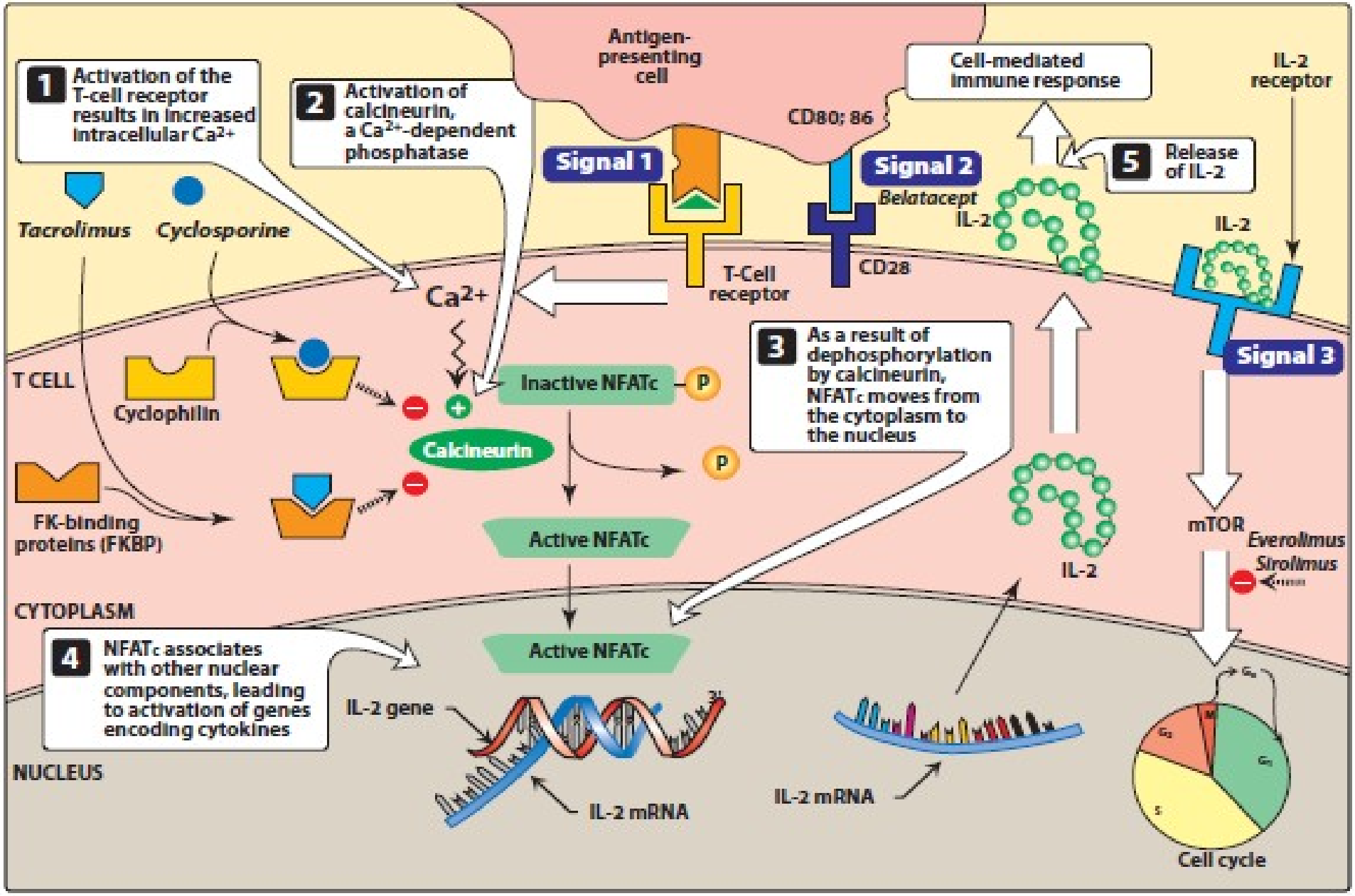

Figure 47.3

Mechanism of action of immunosuppressive *agents*. IL-2 = interleukin-2; mTOR = mammalian target of rapamycin; NFATc = cytosolic nuclear factor of activated T cells; mRNA = messenger RNA.

Pharmacokinetics:

- Cyclosporine may be given either **orally** or by intravenous (**IV**) infusion.
- Oral absorption is variable due to extensive metabolism by a cytochrome P450 (**CYP3A4**) and efflux by P-glycoprotein (P-gp), which limits cyclosporine absorption by pumping the drug back into the gut lumen.
- Excretion of the metabolites is primarily through the **biliary** route into the feces.

Therapeutic Uses:

- ***Cyclosporine*** is used to prevent rejection of kidney, liver, and cardiac allogeneic transplants and is typically combined in a double-drug or triple-drug regimen with *corticosteroids* and an *antimetabolite* such as *mycophenolate mofetil.*

- ***Cyclosporine*** may also be used for recalcitrant psoriasis.

Adverse effects:

Many of the adverse effects caused by *cyclosporine* are **dose dependent.** Therefore, it is important to monitor blood levels of the drug.

- **Nephrotoxicity** is the most common and important adverse effect of cyclosporine, and it is critical to monitor kidney function.
  - **Reduction** of the cyclosporine dosage can result in reversal of nephrotoxicity in most cases.
  - **Coadministration** of drugs that also can cause kidney dysfunction, such as aminoglycosides and nonsteroidal anti-inflammatory drugs, can potentiate the nephrotoxicity of

- *Be*cause **hepatotoxicity** can also occur, liver function should be periodically assessed.
- **Infections** are common and may be life threatening.
  - Viral infections due to the herpes group and cytomegalovirus (**CMV**) are prevalent.
  - **Lymphoma** may occur.
  - **Hypertension.**
  - **Hyperlipidemia.**
- **Hyperkalemia** (K+-sparing diuretics should be avoided in these patients).
  - **Tremor.**
  - **Hirsutism.**
  - **Glucose intolerance.**
  - **Gum hyperplasia.**

B. Tacrolimus

Mechanism of action:

- **Tacrolimus** exerts its immunosuppressive effects in the same manner as *cyclosporine*, except that it binds to a different **immunophilin.**
- **FKBP-12** (**FK**-**b**inding **p**rotein), and the complex then binds to **calcineurin**.

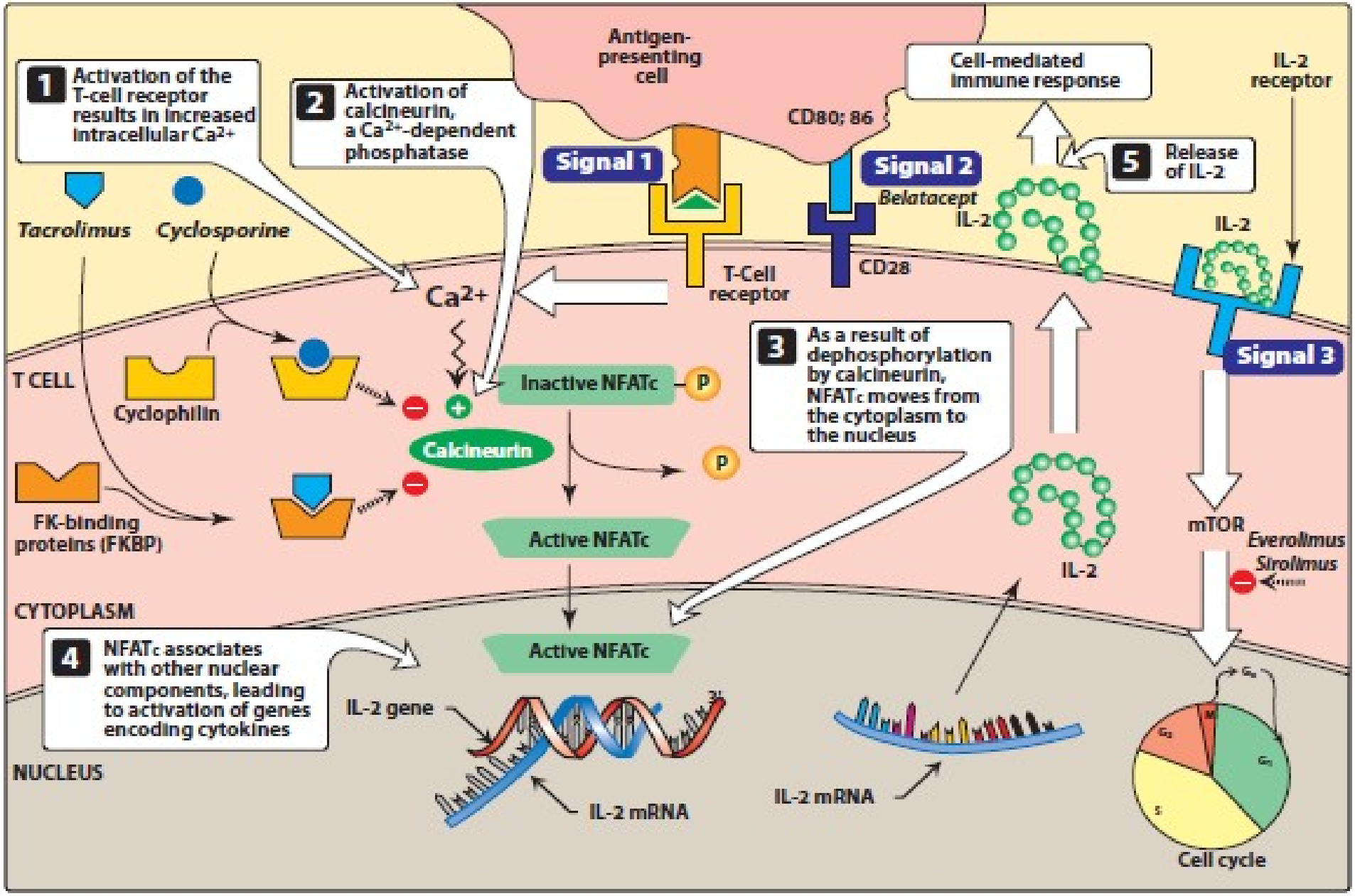

Figure 47.3

Mechanism of action of immunosuppressive *agents*. IL-2 = interleukin-2; mTOR = mammalian target of rapamycin; NFATc = cytosolic nuclear factor of activated T cells; mRNA = messenger RNA.

Pharmacokinetics:

- *Tacrolimus* may be administered **orally** or **IV**.
- The oral absorption of tacrolimus is incomplete and variable due to metabolism by **CYP3A 4/5** isoenzymes and efflux by P-gp.
- Absorption is decreased if the drug is taken with high-fat or high-carbohydrate meals.
- The drug and its metabolites are primarily eliminated in the feces.

Therapeutic uses:

- *Tacrolimus* is currently approved for preventing liver and kidney rejections (along with glucocorticoids).
- It is also used in heart and pancreas transplants.
- An ointment preparation is approved for moderate to severe atopic dermatitis unresponsive to conventional therapies.

Adverse effects:

- Nephrotoxicity and neurotoxicity (tremor, seizures, and hallucinations) tend to be more severe with *tacrolimus* than with *cyclosporine,* but careful dose adjustment can minimize this problem.

- Development of post-transplant insulin-dependent diabetes mellitus is a problem, especially in black and Hispanic patients.

- Other toxicities are similar to *cyclosporine*, except that *tacrolimus* does not cause hirsutism or gingival hyperplasia, but it can cause alopecia.

g Interactions of Calcineurin inhibit

❖Clearance of cyclosporine and tacrolimus is enhanced by co-administration of CYT P450 inducers *(Phenobarbitone, Phenytoin & Rifampin)* → rejection of transplant.

- ❖ Clearance of cyclosporine and tacrolimus is decreased when it is co-administered with (*erythromycin or Ketoconazole, Grapefruit juice)* → tacrolimus toxicity.

Tacrolimus is more favorable than Cyclosporine due to:

- Tacrolimus is 10 – 100 times more potent than Cyclosporine in inhibiting immune responses.
- Compared with cyclosporine, tacrolimus has a lower incidence of cardiovascular toxicities, such as hypertension and hyperlipidemia.
- Tacrolimus has decreased episodes of rejection.
- Tacrolimus is combined with lower doses of glucocorticoids.

But Tacrolimus is more nephrotoxic and neurotoxic.

. Immunosuppressive Antimetabolit

A. Azathioprine

Mechanism of action:

- *Azathioprine* was the **first** agent to achieve widespread use in organ transplantation.
- It is a **prodrug** that is converted first to 6 mercaptopurine then to 6-mercaptopurine nucleotide, thioinosinic acid (nucleotide analog).
- Inhibits de novo synthesis of **purines** required for lymphocytes proliferation.

Therapeutic Uses:

- kidney, liver and cardiac transplants.
- Acute glomerulonephritis.
- Systemic lupus erythematosus.
- Rheumatoid arthritis.
- Crohn’ s disease.

Adverse effects:

- Bone marrow suppression.
- Nausea and vomiting.
- Hepatotoxicity.
- Increased risk of infections.

Drug Interactions:

- Concomitant use with angiotensin-converting enzyme inhibitors or *cotrimoxazole* in renal transplant patients can lead to an **exaggerated leukopenic response.**
- Co-administration of allopurinol with azathioprine may lead to toxicity due to inhibition of xanthine oxidase by allopurinol.
- Allopurinol, an agent used to treat gout, significantly inhibits the metabolism of azathioprine. Therefore, the dose of azathioprine must be reduced.

B. Mycophenolate Mofetil

Mycophenolate mofetil has, for the most part, replaced azathioprine because of its safety and efficacy in prolonging graft survival.

Mechanism of action:

- Prodrug, It is rapidly hydrolyzed in the GI tract to mycophenolic acid, inhibits *de novo* synthesis of purines.
- Mycophenolic acid is a potent, reversible, noncompetitive inhibitor of **inosine monophosphate dehydrogenase (IMP).** It blocks the de novo formation of guanosine phosphate. Crucial for **purine synthesis** → deprivation of proliferating T and B cells of nucleic acids.

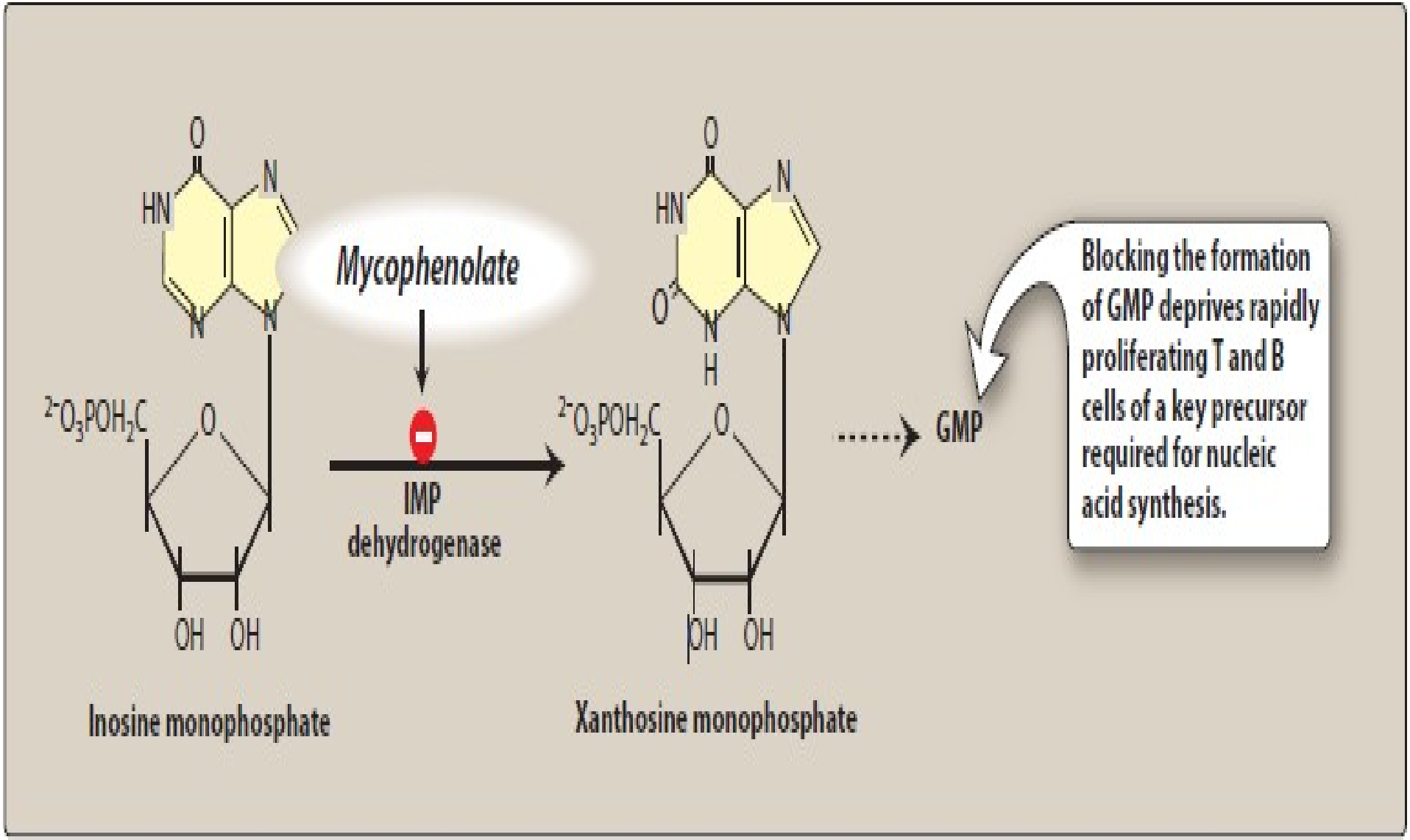

Figure 47.6

Mechanism of action of *mycophenolate*. GMP = guanosine monophosphate.

Pharmacokinetics:

- Given **orally**, **IV** or **IM**.
- Mycophenolic acid is rapidly and **almost completely absorbed** after oral administration.
- It undergoes first-pass metabolism to give the active moiety, mycophenolic acid (**MPA**).
- Metabolized in the **liver**.
- Excreted in **urine**.

Therapeutic uses:

- It has been successfully used in heart, kidney, and liver transplants.
- Steroid-refractory hematopoietic stem cell transplant patients.
- Rheumatoid arthritis, & dermatologic disorders.

Adverse effects:

- GIT toxicity: Nausea, Vomiting, diarrhea and abdominal pain.
- High doses of mycophenolate mofetil are associated with a higher risk of CMV infection.
- Leukopenia, neutropenia.

Drug Interactions:

- Concomitant administration with antacids containing magnesium or aluminum, or with *cholestyramine,* can decrease absorption of the drug.

III. Inhibitors of cytokine gene expression (Corticosteroids)

The corticosteroids were the first pharmacologic agents to be used as immunosuppressives, both in transplantation and in various autoimmune disorders.

For transplantation, the most common agents are *prednisone* and *methylprednisolone*, whereas *prednisone* and *prednisolone* are used for autoimmune conditions.

In transplantation, they are used in combination with agents described previously.

III. Inhibitors of cytokine gene expression (Corticosteroids)

Mechanism of action:

The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear.

The **T lymphocytes** are affected most. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution.

On entering cells, they bind to the **glucocorticoid receptor**.

The complex passes into the nucleus and regulates the transcription of DNA. Among the genes affected are those involved in inflammatory responses.

Therapeutic uses:

- **Solid organ allografts.**
- **Haematopoietic stem cell transplantation.**
- **Autoimmune diseases:**
  - Refractory rheumatoid arthritis
  - Systemic lupus erythematosus
  - Temporal arthritis
  - Asthma

Lecture Quiz

MCQ

Lecture Quiz

Which of the following drugs specifically inhibits calcineurin in the activated T lymphocytes?

A. Azathioprine.
B. Tacrolimus.
C. Prednisone.
D. Mycophenolate mofetil.
E. Methylprednisolone.

B. Tacrolimus.

Lecture Quiz

Which of the following drugs used to prevent allograft rejection can cause hyperlipidemia and hyperkalemia?

A. Cyclosporine.
B. Azathioprine.
C. Prednisone.
D. Mycophenolate mofetil.
E. Methylprednisolone.

A. Cyclosporine.

Lecture Quiz

Which of the following drugs Inhibits de novo synthesis of purines required for lymphocytes proliferation?

A. Azathioprine.
B. Tacrolimus.
C. Prednisone.
D. Cyclosporine.
E. Methylprednisolone.

A. Azathioprine.

Lecture Quiz

GIT toxicity and leukopenia are side effects of one of the following immunosuppressant drug?

A. Cyclosporine.
B. Tacrolimus.
C. Prednisone.
D. Mycophenolate mofetil.
E. Methylprednisolone.

D. Mycophenolate mofetil.

Summary

Mechanism of action of calcineurin inhibitors:

-Cyclosporine binds to a cyclophilin while Tacrolimus binds to a different immunophilin (FKBP-12) to form a complex that binds to calcineurin, cyclosporine–calcineurin complex cannot perform dephosphorylating NFATc leading to decrease in IL-2.

Adverse effects of calcineurin inhibitors:

-Nephrotoxicity,hypertension ,hyperkalemia, hyperlipidemia, tremors, hirsutism, glucose intolerance, gum hyperplasia are side effects of Cyclosporins.

Summary

Drug Interactions of Cyclosporine and Tacrolimus :

❖Clearance of Cyclosporine and Tacrolimus is enhanced by co-administration of CYT P450 inducers *(Phenobarbitone, Phenytoin & Rifampin)* → rejection of transplant.

❖Clearance of Cyclosporine and Tacrolimus is decreased when it is co-administered with (*erythromycin or Ketoconazole, Grapefruit juice)* → tacrolimus toxicity.

Summary

Mechanism of action of Azathioprine:

-Azathioprine It is a prodrug that is converted first to 6 mercaptopurine then to 6-mercaptopurine nucleotide, thioinosinic acid (nucleotide analog).

-Inhibits de novo synthesis of purines required for lymphocytes proliferation.

Mechanism of action of Mycophenolate Mofetil:

-Prodrug, it is rapidly hydrolyzed in the GI tract to mycophenolic acid.

-Inhibits de novo synthesis of purines.

Adverse effects of Immunosuppressive Antimetabolite:

-GIT toxicity, bone marrow inhibition and increase risk of infection.

Mechanism of action of Corticosteroids:

-Bind to glucocorticoid receptors and the complex

SUGGESTED TEXTBOOKS

1- Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2- Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

THANK YOU